PERIODICUM BIOLOGORUM
VOL. 115, No 2, 135–138, 2013

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Critical overview

Stress and pain in emergency and trauma patients

VIŠNJA NESEK ADAM[1]
VIVIANA MRŠIĆ[1]
MARTINA MATOLIĆ[1]
DINKO TONKOVIĆ[1]
ŽARKO RAŠIĆ[2]
TOMISLAV MATEJIĆ[2]

[1]University Department of Anesthesiology, Resuscitation and Intensive Care Clinical hospital Sveti Duh, Sveti Duh 64, Zagreb, Croatia

[2]University Department of Surgery, Clinical hospital Sveti Duh Sveti Duh 64, Zagreb, Croatia

Correspondence:
Višnja Nesek Adam
University Department of Anesthesiology, Resuscitation and Intensive Care, Clinical hospital Sveti Duh, Sveti Duh 64, Zagreb, Croatia
E-mail: visnja.nesek@hotmail.com

Key words: pain, trauma patients, emergency department

Received May 15, 2013.

INTRODUCTION

The International Association for the Study of Pain defines pain as, "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage *(1)*. Pain is the most common reason due to which patients come to the emergency department (ED) and it accounts for more than two-thirds of visits *(2, 3)*. Painful traumatic injuries also account for a large portion of emergency department visits. Improved pain management has not only led to increased comfort in trauma patients, but has also been shown to reduce morbidity and improve long-term outcomes. Untreated or inadequately treatedp pain intensifies the effect of trauma on respiration, hemodynamic stability, renal and gastrointestinal function, leading to an increase in complications and deaths. Therefore, appropriate pain management should be considered a routine part of trauma care and should be given the same attention and resources as other medical conditions.

However, despite widely acknowledged that acute pain management should be an important part of the ED, literature shows that acute pain is not always treated systematically and sufficiently worldwide in EDs. In a observational multicentre study of the Pain and Emergency Medicine Initiative (PEMI) published in 2007 *(4)* 60% of patients admitted to ED received no pain medication and the mean time to administration after arrival stretched to well over an hour (median 90 minutes, range 0–962 minutes) The authors concluded that moderate to severe acute pain is inadequately managed in the ED.

Despite the growing number of pain research study and significant improvements in the pain management in emergency medicine numerous studies continue to affirm that pain management in the ED is insufficient Wilson et al. *(5)* reported that only 44% of patients presenting to an ED with pain received pain medication, Whipple et al. *(6)* reported that 74% of multi-trauma patients received poor analgesia and rated their pain intensity as moderate to severe pain, while Ulvik et al. *(7)* reported that up to 58% of polytrauma patients complaining of diminished quality of life and continuous pain or discomfort up to 2 years post-injury.

There are many and various reasons for deficiencient pain management in ED which include cultural, social, religious, and political attitudes, preoccupation with the diagnosis and treatment of underlying medical problem, ED overcrowding, concern about masking symptoms, poor communication, inadequate knowledge and formal training in acute pain management, lack of routine pain assessment, opiophobia and personal biases or fear of prescription drug abuse. The term opiophobia was introduced in 1985 *(8)*, and now is commonly

used in literature to describe a general unwillingness of physicians to prescribe opiates to patients in severe pain due to the concern that a patient under their care will become an addict. The term "oligoanalgesia" has been used to described the phenomenon of poor pain management through the underuse of analgesia. One of the first studies reporting oligoanalgesia in the ED is the aforementioned retrospective study of Wilson *et al. (5)* Few years later, Lewis *et al. (9)* published a retrospective study of 401 patients treated for acute bone fractures in eight emergency departments; they found that only 30% patient received analgesia and concluded that oligoanalgesia was more the rule rather than exception

MECHANISM OF ACUTE PAIN IN TRAUMA PATIENTS

Acute pain in trauma patients results from tissue damage mainly due to excessive nociception which is usually caused by combination of various stimuli, mechanical thermal or chemical secondary to an inflammatory reaction, a trauma or a visceral lesion. This stimuli cause release of chemical substances (histamine, bradykinin, serotonin, substance P) that activate nociceptors. Once stimulated, a nociceptor transmits a signal along the spinal cord to the brain and causes nociceptive pain. Although acute pain in trauma patients has some useful features such as protective function, acting as a warning sign and preventing further injury, it is well known that injury and pain evokes a wide range of of neuroendocrinologic, haematologic and immunologic changes so called stress response. When the stress of pain becomes severe enough to produce distress, it becomes a stressor as well *(10)*. Thus pain, as both a stress and a stressor, may intensify the physiologic stress response to injury. The efferent pathways of this response begins by activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system which results in secretion of ACTH, cortisol, catecholamines, aldosterone, arginine vasopressine (AVP) and glucagon *(11)*. The increased sympathetic activity results in increased myocardial oxygen demand, reduced myocardial oxygen supply and well recognized cardiovascular effects of tachycardia and hypertension. All of the aforementioned hormonal changes lead to increased catabolism which mobilizes substrates to provide energy sources, and a mechanism to retain sodium and water and rise in heart rate, blood pressure to maintain fluid volume and cardiovascular homeostasis. Other changes during the trauma stress syndrome includes impaired coagulability favouring coagulation and thrombosis and an altered immune response. Depression of immune function after trauma appears to be associated with clinical consequences, including increased rate of nosocomial infection, systemic sepsis and generation of systemic inflammatory response syndrome. The magnitude and duration of the stress is variable and proportional to the severity of injury and pain and accounts for a large portion of the mortality in trauma patients. It is important to note that the stress response after trauma is greater than the stress response after elective surgery *(12, 13)*.

Pain assesment

Insufficient pain control, as we mentioned before, has been correlated with a catabolic stress response as well as increased incidences of venous thromboembolic events, pulmonary complications, and immunosuppression. Therefore, comprehensive pain assessment is one of the most important initial steps for successful management of acute pain in trauma patients and prevention of these complications.

This is usually done by using a simple scale, most often a numeric scale of "0 – 10"or by face scale represented by several illustrations of faces with expressions. Unfortunately, some trauma patients cannot provide a self-report of pain verbally, in writing, or by other means, such as finger span, head movement, pointing, or blinking their eyes to answer yes or no questions *(14)*. Inability to provide adequate pain assessment makes these patients particularly vulnerable to under-recognition and under or over-treatment. Also, trauma patients with the same injury may show a completely different intensity of pain due to genetics, gender, age, emotional state and personal history to differences in pain sensitivity. Although the physiological markers of sympathetic activation can be very useful in pain assessment very often do not correlate well with the degree of injury and pain. Therefore, careful selection of an effective analgesic regimen should be based on the type and amount of patient' pain rather than specific injuy. A Hierarchy of Pain Assessment Techniques has been recommended as a framework to guide assessment approaches and is relevant for patients unable to self-report *(15, 16)*.

Pain therapy

The primary aim of acute pain management in trauma patients is to minimize pain through the careful use of drugs and pain interventions, improve function and increase quality of life while avoiding side effects. There are a variety of different therapies and techniques available for acute pain relief which arises from multidisciplinary approach. This multi-modal approach usually includes pharmacological interventions with conventional analgesics, but the use the regional anaesthetic techniques, adjuvant agents and non-pharmacological methods can also be very usufull in acute pain management in ED.

Pharmacological interventions

Conventional analgesics

Conventional analgesics include paracetamol (acetaminophen), non-steroidal antiinflammatory drugs (NSAIDs), weak and strong opioids. They provide the basis for the pain treatment especially for acute pain in prehospital emergency medicine and emergency department.

Paracetamol (acetaminophen)

Paracetamol is a widely used analgesic and antipyretic without peripheral anti-inflammatory effects. Although the exact mechanisms of action are still unclear, para-

cetamol appears to produce analgesia by raising the pain threshold, predominantly through a central rather than peripheral mechanism *(16)*. It is thought that paracetamol perform its analgesic activity by inhibiting the synthesis of prostaglandins in the CNS (central acting) and peripherally blocking pain impulse generation *(17)*. Paracetamol is classified as a mild analgesic and an adjunct to opioids in more severe pain. It is not associated with the increased incidence of nausea, vomiting, and respiratory depression that can occur with opioids, or the platelet dysfunction, gastritis, and renal toxicity that are sometimes associated with NSAIDs. Paracetamol is the only approved IV nonopioid analgesic that does not include a boxed warning on the label. In November 2010, the U.S. Food and Drug Administration (FDA) approved IV acetaminophen for the management of mild to moderate pain, for the management of moderate to severe pain with adjunctive opioid analgesics and for the reduction of fever in adults and children (age =2 years) *(18)*. The above mentioned characteristics and speed of onset makes IV acetaminophen particularly suitable in emergency settings.

Nonsteroidal anti-inflammatory drugs (NSAIDs) include nonselective NSAIDs and the selective cyclooxygenase (COX-2) inhibitors. The most commonly available and used NSAIDs are from the propionic acid (ibuprofen, naproxen) and acetic acid (indomethacin, ketorolac, diclofenac) derivative classes. The primary mechanism by which NSAIDs exert their effects is via inhibition of 2 distinct pathways mediated through COX-1 and COX-2. Both enzymes (COX-1 and COX-2) produce prostaglandins that stimulate inflammation, pain, and fever; while COX-1 also produces prostaglandins that activate platelets and protect the stomach and intestinal lining. NSAIDs block the COX enzymes and prevent the synthesis of prostaglandin and thus reduce pain and inflammation.

NSAIDs are widely used in a variety of acute pain settings for their anti-inflammatory and analgesic effects. However, as a group thay are responsible for more serious side effects than any other class of analgesic drug *(19)*. The major side effects of NSAID are gastrointestinal bleeding, renal failure, anaphylaxis, and platelet dysfunction. Traditional NSAIDs are contraindicated for posttraumatic analgesia because of the aforementioned inhibition of platelets and bleeding potential which can be especially harmful for patients with major traumatic injuries *(20)*. Selective cyclooxygenase inhibitors (coxibs) do not inhibit platelets and treatment with selective COX-2 inhibitors do not increase the risk of bleeding so, they can be used in these settings *(21, 22)*. In addition, NSAIDs are commonly used for managing mild to moderate pain while in most trauma patients injuries are too severe to be relieved by NSAIDS alone.

Regular, NSAIDs can be used in trauma patients with no risk of bleeding as part of multimodal approach. When NSAIDs alone cannot control pain, they can be used in combination with opioids. The concurrent use of opioids and NSAIDs often provides more effective analgesia than either of the drug classes alone and also opioid-sparing effect of NSAIDs reduces the risk of opioid adverse events such as respiratory depression and ileus.

Opiod

Opioid analgesics remain cornerstone of the management of moderate to severe pain because of their potent efficacy. They produce pharmacologcal actions by acting on receptrors located on neuronal cell membranes. Opioids bind to specific endorphin receptors that suppress the detection of pain peripherally, modify pain transmission in the spinal cord and thalamus, and alter the perception of pain in the cortex. There are several types of opioids and the most commonly used are morphine, meperidine, fentanyl, and hydromorphone. There is no conclusive evidence to suggest that there are any significant differences in efficacy or side effect profiles between any of the pure opioids when applied at equianalgesic doses. But for some reasons, that are probably the result of differences in the pharmacokinetics and pharmacodynamics, some opioids may be more effective than others in individual patients *(22)*. About 10% of patients are unable to covert enough codeine or tramadol to the active opioid metabolite (morphine or M1) needed for analgesic response and these patients are at risk of analgesic failure *(23)*.

All opioid drugs are characterized by dose-dependent analgesia as well as dose-dependent side effects. The side effects include sedation, respiratory depression, constipation, urinary retention, nausea or vomiting, pruritus and urticaria.

Current literature data show large variations in initial dosing of the most commonly used opioids and also show that the optimum dose remains very controversial among ED physicians. Morphine can provide an example of these controversies associated with the optimum dose. Morphine is the most commonly used strong opioid in the acute pain setting and is a first line agent in the management of pain after major trauma and in ED. The American Pain Society recommends an initial dose of morphine 0.1–0.15mg/kg, or 5–10 mg if weight is above 50 kg within 15–20 minutes followed of 0.05 mg/kg given every 5 minutes until pain is relieved. Hovewer, Bijure et al. *(24)* showed that only 67% of patients who received this dose reported less than 50% reduction in pain 30 minutes after administration which means that these doses are not sufficient to treat severe pain. Birnbaum et al. *(25)* also reported less than 50% of the effectiveness of opioid therapy1 hour after administration of 0.1 mg/kg of morphine. Therefore for each patient, the treatment with morpine and any of opioids should be individualized taking into account intensity of pain, severity of injury, level of consciousness, hemodynamic instability, age, other medications, previous exposure to opioids and presence of coexisting disease.

The most suitable opioid in critically ill trauma patients is fentanyl. Fentanyl is a synthetic opioid 50 to 100 times more potent than morphine. Although, it has been

associated with respiratory depression more frequently than morphine it causes less histamine release and peripheral vasodilation. Fentanyl may be a more suitable option in acute pain management of trauma patients because it causes less hemodynamic instability.

Regional anesthesia

Regional anesthesia has been growing in popularity for the treatment of the acutely injured patient. Regional technique provide not only excellent analgesia, but also reduce sedative medication, opioid-related side effects such as nausea, vomiting, pruritis, constipation and urinary retention, decrease risk of hypotension compared to some conscious sedation techniques especially if the patient is hypovolemic and attenuates stress response to injury. In addition, several studies have shown decreased ICU and hospital length of stay, decreased infection rate, increased cardiac and pulmonary function, significant decreased in hypercoagulable-related events and earlier recovery of postoperative gastrointestinal function *(26, 27, 28)*. However, it must be emphasized that although regional analgesia offers many benefits, it also carries some risks arising from technical complexity of procedures and lack of knowledge by providers in the prehospital and emergency department. Complications arising from regional techniques in these patient include local anesthetic toxicity, nerve and vascular injury, pneumotorax, infection and the possibility of masking a the development of compartment syndrom. Some studies have confirmed a greater risk of complication in outpatient surgery population and critically ill patient *(29)*.

Regional anesthesia can improve outcomes in trauma patients when applied judiciously, but the risk must be weighed against the benefits because these patients may present with a spectrum of injuries and in various degrees of shock.

CONCLUSION

Pain is the most common reason due to which patients come to the emergency department and painful traumatic injuries account for a large portion of emergency department visits. Inadequately managed pain can lead to adverse physical and psychological patient outcomes. Because of the capricious nature of trauma pain, recognition and alleviation of pain, regular assessment and frequent adjustments in medications, dosages, and techniques should be a priority when treating the ill and injured patients.

REFERENCES

1. MERSKEY H, BOGDUK N 1994 Classification of Chronic Pain, IASP Task Force on Taxonomy. IASP Press, Seattle.
2. CORDELL W H, KEENE K K, GILES B K, JONES J B, JONES J H, BRIZENDINE E J 2002 The high prevalence of pain in emergency medical care. *Am J Emerg Med 20(3):* 165–9
3. TANABE P, BUSCHMANN M 1999 A prospective study of ED pain management practices and the patient's perspective. *J Emerg Nurs 25:* 171–7
4. TODD K H, DUCHARME J, CHOINIERE M, CRANDALL C S, FOSNOCHT D E, HOMEL P et al 2007 Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. *J Pain 8(6):* 460–6
5. WILSON J E, PENDLETON J M 1989 Oligoanalgesia in the emergency department. *Am J Emerg Med 7(6):* 620–3
6. WHIPPLE J K, LEWIS K S, QUEBBEMAN E J, WOLFF M, GOTTLIEB M S, MEDICUS-BRINGA M, HARTNETT K R, GRAF M, AUSMAN R K 1995 Analysis of pain management in critically ill patients. *Pharmacotherapy 15:* 592–9
7. ULVIK A, KVALE R, WENTZEL-LARSEN T FLAATTEN H 2008 Quality of life 2–7 years after major trauma. *Acta Anaesthesiol Scand 52:* 195–201
8. MORGAN J P 1985 American opiophobia: customary underutilization of opioid analgesics. *Adv Alcohol Subst Abuse 5(1–2):* 163–73
9. LEWIS L M, LASATER L C, BROOKS C B 1994 Are emergency physicians too stingy with analgesics? *South Med J 87:* 7–9
10. Committee on Pain and Distress in Laboratory Animals, Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, Recognition and Alleviation of Pain and Distress in Laboratory Animals 1992, National Academy Press, Washington, DC
11. DESBOROUGH J P, HALL G M 1993 Endocrine response to surgery. *In:* Kaufman L. Anaesthesia Review, Vol. 10. Edinburgh, Churchill Livingstone, 131–48
12. MALCHOW R J, BLACK I H 2008 The evolution of pain management in the critically ill trauma patient: Emerging concepts from the global war on terrorism. *Crit Care Med 36:* 7 (Suppl.) S346–57. doi: 10.1097/CCM.0b013e31817e2fc9
13. COHEN S P, CHRISTO P J, MOROZ L 2004 Pain management in trauma patients. *Am J Phys Med Rehabil 83:* 142–61
14. HERR K, COYNE P J, MANWORREN R, MCCAFFERY M, MERKEL S, PELOSI-KELLY J, WILD L 2006 Pain Assessment in the Nonverbal Patient: Position Statement with Clinical Practice Recommendations. *Pain Manag Nurs 7(2):* 44–52
15. PASERO C, McCAFFERY M 2011 Pain assessment and pharmacologic management. Elsevier, St. Louis,342 MO, Mosby.
16. RAFFA R B, STONE D J, TALLARIDA R J 2001 Unexpected and pronounced antinociceptive synergy between spinal acetaminophen (paracetamol) and phentolamine. *Eur J Pharmacol 412:* R1–2
17. PASERO C, STANNARD D 2012 The Role of Intravenous Acetaminophen in Acute Pain Management. A Case-Illustrated Review. *Pain Manag Nurs 13(2):* 107–24
18. CADENCE PHARMACEUTICALS 2010 Ofirmev (acetaminophen) injection. Cadence Pharmaceuticals, San Diego, CA,
19. HERSH E V, PINTO A, MOORE P A 2007 Adverse drug interactions involving common prescription and over-the-counter analgesic agents. *Clin Ther 29:* 2477–97
20. PERTUSI R 2004 Selective cyclooxygenase; inhibition in pain management. *J Am Osteopath Assoc 104:* 19–24
21. ZEMMEL M H 2006 The role of COX-2 inhibitors in the perioperative setting: Efficacy and safety – A systematic review. *AANA J 74:* 49–60
22. KEENE D D, REA W E, ALDINGTON D 2011 Acute pain management in trauma. Trauma 13(3): 167–79
23. DESMEUALES J A 2000 The tramadol option. *Eur J Pain 4(suppl):* 15–21
24. BIJUR P E, KENNY M K, GALLAGHER E J 2005 Intravenous morphine at 0.1 mg/kg is not effective for controlling severe acute pain in the majority of patients. *Ann Emerg Med 46:* 362–7
25. BIRNBAUM A, ESSES D, BIJUR P E, HOLDEN L, GALLAGHER E J 2007 Randomized double-blind placebo-controlled trial of two intravenous morphine dosages (0.10 mg/kg and 0.15 mg/kg) in emergency department patients with moderate to severe acute pain. *Ann Emerg Med 49:* 445–53
26. MODIG J, BORG T, KARLSTROM G, MARIPUU E, SAHLSTEDT B 1983 Thromboembolism after total hip replacement: role of epidural and general anesthesia. *Anesth Analg 62:* 174–80
27. LIU S, CARPENTER R L, NEAL J M 1995. Epidural anesthesia and analgesia: their role in postoperative outcome. *Anesthesiology 82:* 1474–506
28. NESEK ADAM V, MARKLÆ A, \AKLÆ K, GRIZELJ STOJÈLÆ E, MR\LÆ V, TONKOVLÆ D 2011 Local anaesthetic toxicity. *Period Biol 113:* 141–6
29. GREENSMITH J E, MURRAY W B 2006 Complications of regional anesthesia. *Curr Opin Anaesthesiol 19:* 531–7